The Infectious Aspects of Atopic Dermatitis

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KEYWORDS

• *S aureus* • Eczema herpeticum • Eczema vaccinatum
• Superantigen • Toll-like receptors • Malassezia

Atopic dermatitis (AD) is a chronic inflammatory skin disease that causes significant morbidity in affected individuals. The disease is often characterized by chronic inflammation and pruritus interrupted by acute flares and bacterial infection.[1] AD results in significant sleep loss, poor school/work performance, and disruption of social activities. In addition, severe AD patients are at risk for rare invasive bacterial infections and life-threatening eczema herpeticum (EH).[2,3] Although recent studies have provided strong support for the basis of skin barrier defects in the pathogenesis of AD,[4] the cause of AD remains incompletely understood. More recent data have also provided further insights into the important role of immune responses in the pathogenesis of AD (**Table 1**). Of note, AD patients with increased allergic responses have more severe skin disease and a greater tendency to suffer from skin infections. These studies provide evidence for a role of the immune response in the expression of AD. Secondary skin infections have long been known to be associated with AD flare. The most common skin infections in AD are caused by *Staphylococcus aureus* and herpes simplex virus (HSV). In the absence of clinical signs of infections, most AD patients are also colonized with *S aureus* on their skin lesions. This pathogen is known to produce a myriad of proinflammatory factors that may trigger the cutaneous immune system.[5] In this review, the authors discuss

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Table 1
Recent developments in the infectious aspects of AD

Filaggrin gene mutations facilitate IgE expression in a mouse model[20]
Toll-like receptor genetic polymorphisms may lead to cytokine dysregulation and inflammation in AD[45–47]
Emerging roles of nonclassical staphylococcal superantigens (SEE and SEG-SEQ) and methicillin-resistant *Staphylococcus aureus* in the pathogenesis of AD[5,58,59]
AD patients with specific IgE sensitization or other atopic diseases including asthma and food allergy are at increased risk for viral skin infections[67]
Innate immune response genes including leukotriene B4 receptor (LTB4R), orosomucoid 1 (ORM1), coagulation factor II (thrombin) receptor (F2R), complement component 9 (C9), lipopolysaccharide binding protein (LBP), and leucine-rich repeat protein 1 (NLRP1) may be involved in the pathogenesis of vaccinia virus infection in AD[74]

recent developments in the genetic basis of skin barrier, immune phenotypes, and the role of microbial pathogens in AD.

SKIN BARRIER DEFECTS IN THE PATHOGENESIS OF AD

The stratum corneum (SC) of the skin acts as an important barrier in preventing water loss from the skin and in protecting the skin from intrusion by irritants or microbes. Based mainly on transepidermal water loss (TEWL) studies, the SC of AD skin has been found to be defective. The TEWL in AD lesions is significantly greater as compared with nonlesional AD skin and healthy skin.[6,7] In addition, it has been shown that nonlesional AD skin has greater TEWL and significantly thinner SC than healthy skin (12.2 μm vs 19.7 μm).[8] Increased TEWL correlates with increased AD severity.[9] Various proteins and lipids responsible for skin barrier function have been found to be deficient in AD skin. These molecules include filaggrin, involcrin, cholesterol, free fatty acids, and ceramides.[10,11] More recently, a genetic basis for the skin barrier defect in AD has been demonstrated by the strong association between filaggrin gene mutations and AD.[4] Two loss-of-function mutations in the filaggrin gene (FLG) (R501X and 2282del4) have been linked to childhood-onset AD, particularly in patients who have onset of AD at 2 years or younger.[12] Of patients with onset of AD 2 years or younger, 21.3% had 1 or more FLG mutated alleles, as compared with 15.8% and 9.5% in patients with non-FLG related childhood-onset AD and healthy controls, respectively.[12] These results were also replicated in AD patients with rarer FLG mutations such as R2447X, S3247X, 3702delG, and 3673delC.[13] In addition, it has been shown that patients with early-onset AD and FLG mutations have a tendency to have persistent disease into adulthood.[14] FLG in AD patients was significantly associated with the extrinsic form of the disease (ie, patients with elevated total serum IgE and/or presence of specific IgE against inhalant or food allergens), and the development of allergic rhinitis and asthma.[15–19] The association of IgE sensitization with FLG in AD has recently been supported by a mouse model with a homozygous frameshift mutation in filaggrin that is analogous to human FLG.[20] This mouse model facilitates cutaneous allergen sensitization that leads to production of specific IgE. Although the association of FLG with AD and atopy is clear, the role of FLG in modifying immune response in human AD has not been established. Of note, approximately 40% of carriers of FLG mutations showed no sign of AD.[4] Indeed, FLG mutations were initially found to be the cause of ichthyosis vulgaris, which is a dry skin condition with no apparent inflammation or infection.[21] Therefore, additional factors must be involved in the pathogenesis of AD.